UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,518	07/06/2001	Keith D. Allen	R-716	3954

26619 7590 12/15/2005

JOHN E. BURKE
GREENBERG TRAURIG LLP
1200 17TH STREET, SUITE 2400
DENVER, CO 80202

EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,518	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X. Qian Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-32,36,38,39,42,43 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-32,36,38,39,42,43 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-32, 36, 38, 39, 42, 43 and 46 are pending in the application.

This Office Action is in response to the Amendment filed on 9/20/05.

Response to Amendment

The rejection of claims 29-32, 36, 38, 39, 42, 43 and 46 under 35 U.S.C. 101/112 1st paragraph is maintained for reasons set forth of the record mailed on 6/21/05 and further discussed below.

The objection to the specification is maintained for same reason as set forth of the record mailed on 6/21/05 and further discussed below.

Response to Arguments

Claim Rejections - 35 USC § 101

Claims 29-32, 36, 38, 39, 42, 43 and 46 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility.

Claims 29-32, 36, 38, 39, 42, 43 and 46 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to this rejection, Applicants repeats the argument that the claimed invention has well-established utility that is substantial and specific. Further, Applicant asserts that studying the function of the CX2 is a substantial utility because there is no further research required to confirm the utility of the claimed mouse in determining CX2 function because 1) the

value of the knockout mouse is well established in the art; 2) further characterization of the mouse itself is not required to confirm its utility in studying the CX2 function; 3) Applicant has provided an *in vivo* model for studying the function of the CX2 gene which is associated with the claimed phenotype such as cell infiltration. Applicant indicates that the claimed invention is purchased by the large pharmaceutical company satisfies the commercial success criteria because of the recognition of the research tool for drug development. Applicant asserts that the company uses the mouse for the same purpose asserted in the specification. Moreover, Applicants assert that the utility to study CX2 gene function and expression using the claimed mouse is specific to the CX2 gene knockout mouse because no other mouse can be used for this purpose. Furthermore, Applicant argues that the mice within the claim 29 contain a lacZ gene, its use in studying gene expression is recognized in the art as taught by Austin et al. Applicant further asserts that the claimed mouse represents a specific disease since it demonstrates an increase glucose level, thus it has a credible, substantial and specific use as the case *In re Brana*. Further, Applicant asserts that Olsen does not support the position that knockout mouse have no utility, but rather demonstrate that GABA plays a major role in brain development, and rather agree that the claimed mouse has utility since it has phenotype. Applicant further asserts that all behavioral tests were performed using 10 mice while non-behavioral tests were performed using 6 mice were not contradictory, and the credential of the Deltagen employee is highly relevant to the credibility of the reported phenotype and their association with gene function, especially to examiner's questioning of the credibility of asserted utility. Applicant also argues that the so-called hitchhiker effect is considered a rare phenomenon. Moreover, Applicant asserts that there is no evidence that the lacZ-Neo cassette is causing "confounding" phenotypes in the presently

claimed invention, and it is unreasonable to expect the patentee to exclude this possibility. Finally, Applicant concludes the claimed invention has patentable utility.

These arguments have been fully considered but deemed unpersuasive. The reasons for the utility and non-enablement rejection were discussed in detail in the office action mailed on 6/21/05. In response to Applicant's response regarding any knockout mouse has a well-established utility, the examiner does not agree with Applicant's assertion that the claimed invention has a well-established utility. Applicant is reminded that in MPEP, the guideline for the utility requirement clearly states: "An invention has a well-established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process), and (ii) the utility is specific, substantial, and credible." In the instant case, the utility that applies to any knockout mouse is not specific to the claimed invention, the CX2 transgenic mouse having a null allele. It was well known to knock out a gene to determine its function or what will happen when the gene is not expressed. However, scientific "utility" is not the same as "patentable utility" or a "well-established" utility, of which must be specific, substantial and credible. At the time of filing, knockout mice were used for further research in the art as indicated by the quotations cited by Applicant, for example, studying gene function. However, further research does not rise to the level of a "well-established utility" because such a utility is not substantial. The utility guidelines specifically state that further research is not a "substantial utility." The MPEP states "the following are examples of situations that require or constitute carrying out further research to identify

or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities": A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved..." In the instant case, further study of mice would have been required to determine how to use the mouse of applicant's invention according to the embodiments described in the specification since the overall phenotype of the claimed mice does not correlate with any disorder; Therefore, further study would be required to characterize such association because the teaching of the specification is not sufficient to establish whether the phenotype is directly result from the gene disruption. Further study would be required to determine the function of the disrupted gene and its role in the resultant phenotype. Furthermore, the overall phenotype of the claimed mice does not correlate to any disorder; therefore, further study would be required to determine how to use the mice to study a disorder, screening drugs and treatment for such disorder. Thus, using the mice claimed for further research is not a "substantial utility." Applicant's allegation that the examiner has done what MPEP cautions against is groundless unless Applicant provides evidence or reason to support such allegation.

In response to Applicant's argument of the commercial sale of the claimed mouse, Applicant is reminded that the sale of a product does not automatically gives the product patentable use according to the statue of 35 U.S.C.101 and the utility guideline set forth in the MPEP. Commercial success is only considered as secondary evidence for overcoming a 103 (a) rejection according to guidelines set by MPEP. *Brenner v. Manson* does not validate the notion that commercial use automatically gives a claimed product patentable utility. The purchase of

the claimed mouse by a large pharmaceutical company neither proves commercial success of the claimed mouse nor does it gives the claimed mouse a patentable utility. The case law of *Phillips Petroleum Co. v. U.S. Steel Corp.* 6 USPQ 2d 1065 talks about commercial success in context as secondary consideration in favor of nonobviousness (see page 1096). It states "of course, there must be a nexus "between the merits of the claimed invention and the evidence offered if that evidence is to be given substantial weight enroute to conclusion on the obviousness issue." *Stratoflex* , 713 F.2d at 1539 [218 USPQ at 879] (noting *Solder Removal Co. v. United States Intern. Trade* , 582 F.2d 628, 637 [199 USPQ 129, 137] (C.C.P.A. 1978)). Crystalline polypropylene is one of the most widely used chemical compositions in commerce today. Worldwide demand is presently approximately fourteen billion pounds, with the United States' demand totaling nearly six billion pounds per year. (Mark, Tr. at 503.) 68 Experts from both sides were in general agreement that crystallinity is the characteristic which gives polypropylene its immense commercial value." According to the case law, the commercial success is established by the worldwide use of the claimed compositions and the generation of high revenue from the sale of the claimed composition. However, the sale of the present claimed invention to a pharmaceutical company clear does not mount to such "commercial success." Although the mouse is sold to a pharmaceutical company, it is unclear how the company going to use the mouse. There is no evidence that the mouse is going to be used for same purpose as taught in the specification. A single sale of a mouse does not mount to commercial success as asserted by Applicant. As such, this statement about the pharmaceutical company using the mouse for the same utility disclosed in the specification alone does not automatically gives the claimed mouse

a patentable utility. Therefore, based on the utility requirement set forth in MPEP, the sale of the mouse to one company does not give the claimed mouse a patentable utility.

With regard to Applicant's argument about specific utility, the examiner would like to reiterate that using a knockout mouse with a phenotype not necessarily result from the lack of expression of said gene such as caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene. Applicant has not provide sufficient teaching in the specification that the CX2 knockout mouse is a valid model for seizures or any metabolic disease. The Olsen reference and Crawford reference (cited in earlier office action) both teach that the phenotype of a knockout mouse is unpredictable, and there are instances that the observed phenotype is not directly result from the disruption of a specific gene. In view of such unpredictability in the art, the burden is on Applicant to teach such specific correlation does exist in the specification, and thus the claimed mouse is useful as a disease model. Further, Applicant must teach what specific disease(s) the claimed mouse represents. In the instant case, Applicant fails to do both. As discussed above, the overall phenotype does not correlate to any specific disease. The broad assertion of the claimed mouse can be used to study seizure and metabolic disease is not sufficient to establish as substantial and specific use for the claimed mouse. Further, in view of the broad scope of metabolic disorder, which specific disorder the claimed mouse represents is unclear. Therefore, the claimed mouse does not have specific utility.

With regard to Applicant's argument about claim 29, Applicant is again reminded that the specification does not provide sufficient teaching about the function of the CX2, thus studying a expression of a gene of which the function is unknown is not a patentable utility. Further,

according to the disclosure of the specification, it is even unclear whether the expression of the endogenous CX2 can be studied using the claimed mouse. The examiner directs Applicant's attention to page 3, 1st paragraph, which discloses that wild type CX2 expresses in brain, liver, kidney and lung, and page 46, lines 5-10, which discloses a number of tissues that lacZ was not expressed, including brain, liver, kidney and lung. Such finding is rather contradictory to the argument that the claimed mouse can be used to study CX2 endogenous expression.

In response to Applicant's argument regard *In re Brana*, the examiner does not agree that this case law applies to the instant case for same reasons as discussed in the previous office action. Applicant did not address the arguments presented by the examiner but simply repeat the conclusion that the claimed mouse has utility according to *In re Brana*. The examiner presents the same argument below, and Applicant is invited to present specific reasons for the supposed error. In the *Brana* decision, the court concluded that the mouse tumor models (leukemia cell lines were originally derived from lymphocytic leukemia in mice) represent a specific disease against which the claimed compounds were alleged to be effective. As such, the claimed compound has credible, substantial and specific utility. In *Brana*, the asserted utility meets the requirement of the statue because the claimed compounds are effective in a valid and specific mouse tumor model. However, in the instance case, the claimed knockout mouse does not have a credible, substantial and specific use because the specification does not teach what specific disease model the claimed mouse represents and/or what type of drug the claimed mouse can screen. The mere statement that the claimed mouse can be used to study diabetes and other metabolic disorder is not sufficient to establish a

credible, substantial and specific utility for the claimed mouse. The phenotype of the claimed mouse is decreased glucose level in blood after administration of glucose, which is opposite to a diabetic model, wherein the animal cannot metabolize glucose. As such, it cannot be used as a valid diabetic model. The specification fails to teach what other metabolic disorder the claimed mouse represents. Similarly, the specification only discloses that the CX2 knockout mouse displays a decreased threshold to metrazol test. The specification fails to address whether the behavioral phenotype is directly result from the lack of expression of CX2 or secondary to other gene product that may not relate to CX2. Thus, the claimed mouse is not a valid model for seizure. The prior art is silent on the claimed mouse thus does not recognize any well-established utility for the claimed mouse. Moreover, the utility of using the claimed mouse to study CX2 function or association to the phenotype is not a credible, substantial and specific utility for reasons discussed above. Therefore, unlike *Brana,* the instant specification fails to provide a credible, substantial and specific utility for the claimed mouse.

With regard to the well-established utility of studying gene function as asserted by Applicant, Olsen (GABA in the Nervous System, 2000, pg 81-95) taught that "although gene targeting is often useful in delineating the contribution of a given gene product to phenotypic characteristics observed, some gene knockouts lead to embryonic or perinatal lethality, and others lead to no apparent phenotype. This can arise from a lack of any role for the gene in question in regard to the trait studies or from compensation by other gene products. Analysis of the compensation can yield valuable clues to the genetic pathway" (pg 82, last 11 lines of col. 1). As such, a knockout mice may not be capable of elucidating the function of the protein and may

only provide a clue to a pathway the protein being knocked out is involved in. Using the claimed mice to obtain a clue to a pathway is not a "substantial utility." Using a mouse with a phenotype caused by genes compensating for a knocked out gene is not a "specific utility" because the phenotype is not specific to the knocked out gene. The examiner does not agree with Applicant's interpretation of the Olsen reference as teaching knockout mouse has well-established utility, and whether the GABA knockout mouse has well-established utility is beside the point. The relevant issue is whether the claimed mouse having a null CX2 gene has patentable utility. For reasons discussed in the previous office action and above, the claimed mouse does not have patentable utility.

In response to Applicant's argument about the number of mice used in each behavioral experiment, the base line value for the 129, C57BL/6 and F1 hybrid, Applicant is reminded such data are not present in the specification. Applicant is invited to point out specifically in the specification where such teaching is provided. With regard to Applicant's argument with the credential of Deltagen's employee, Applicant is reminded that the examiner questions the utility of the claimed invention based on the disclosure of the specification and the prior art, not information outside of the specification, such as how the pathologists of Deltagen conduct the experiments or what advanced degrees they hold.

Applicant's citation of Wolfer et al. to rebuttal examiner's position of phenotype is may be affected by genetic background is problematic, because Applicant focused on one factor "hitch-hiker allele" which the author regards as a rare phenomenon, but ignores the rest of the discussion about how genetic background of the mouse affects the phenotype. Applicant's attention is directed to page 336, last paragraph through page 337, wherein the different genotype

of the recipient strain contributes to different phenotype of null Fmr1 gene. This actually supports the examiner's position that genetic background of the mouse affects the phenotype.

In response to Applicant's argument of Scariff et al., it is unclear what it Applicant's position regard to the utility requirement. The examiner's position is simply that in view of the art recognized unpredictability, whether the phenotype observed in the mouse is result from the knockout of CX2 is unclear based on the disclosure of the specification. Furthermore, the overall phenotype of the claimed mouse is not indicative if said mouse represents any human disease. As such, for reasons given in the previous office action and above, the specification fails to disclose a credible, substantial and specific use for the claimed mouse and one skilled in the art would not know how to use the claimed mouse according to the embodiments disclosed by the instant specification. Therefore, the 101 rejection is maintained.

In response to the 112 1st rejection, Applicant argues that the claimed invention has utility thus one of skilled in the art would know how to use it. Applicant requests the examiner to explain the comment of "Applicant did not argue the enablement rejection separately" in the previous office action.

The examiner maintains the position that the claimed invention lack patentable utility, thus one of skilled in the art would not know how to use the claimed invention. Moreover, to clarify the previous comment, Applicant is reminded that the 112 1st rejection is not entirely based on the utility rejection discussed above. Applicant's attention is directed to the office action mailed on 7/13/04, wherein additional reasons for lack of enablement of the claimed invention were discussed (see page 4, last paragraph through page 9). This rejection is maintained for same reasons discussed previously and set forth above in the utility rejection.

Specification

In response to the new matter objection, Applicant argues that the only document incorporated by reference is the disclosure of the originally cited 09/971,310 application, wherein US patent no. 6,815,185 is only being cited as a publicly available document which contains the disclosure of 310 application, thus the amendment does not contain new matter.

The above argument has been considered but deemed unpersuasive. The recitation of "using the methods described in U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent No. 09/885,816...which is incorporated herein in its entirety." Such amendment introduces new matter because the disclosure of "U.S. Patent no. 6,815,185 issued November 9, 2004, which is based on U.S. Patent No. 09/885,816..." differs from the original disclosure because the methods described in the 185 patent and 09/885,816, etc is new information although not incorporated by reference. Applicant is remind that new matter does not necessarily has to be incorporated by reference. This objection is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X. Qian Ph.D. whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine X Qian Ph.D.
Examiner
Art Unit 1636

CELIAN QIAN
PATENT EXAMINER